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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NATARAJAN, MEERA	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,997	ZHU, ZHENPING	
	Examiner	Art Unit	
	Meera Natarajan	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *18-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/04/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 1-17 in the reply filed on 07/09/2007 is acknowledged. The traversal is on the ground(s) that "the special technical feature of the present invention is a finding that neutralizing activation of KDR is related to angiogenesis. Neutralizing the activation of KDR is due to human antibodies of the present invention binding to KDR and blocking binding of vascular endothelial growth factor (VEGF) to KDR. Thus, human antibodies of the present invention can be used for treating neoplastic diseases and hyperproliferative disorders. Since the corresponding special technical feature is the neutralizing activation of KDR, applicants believe that the inventions listed as Groups I and II form a single general inventive concept under PCT Rule 13.1". This is not found persuasive because as stated in the restriction requirement the technical feature recited in claim 1, an antibody which binds selectively to KDR, is not special in view of Lu et al. Lu et al. (Int. J. of Cancer 2002 Jan 20; 97(3):393-9) teach a human antibody that binds selectively to KDR and therefore reads on Claim 1. In addition Claim 1 does not disclose neutralizing the activation of KDR. The requirement is still deemed proper and is therefore made FINAL.

2. Claims 18-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/09/2007.

3. Claims 1-17 will be examined on the merits.

Specification

4. The disclosure is objected to because of the following informalities: The first line of the specification claims priority to U.S. Provisional Application No. 60/361,783, however the date associated with the provisional "March 4, 2003" is incorrect. The disclosure should be corrected to show the correct date March 4, 2002.

Claim Objections

5. Claim 5 is objected to because of the following informalities: Claim 5 recites "antobody" in line 1. Appropriate correction is required.

Claim Rejections - 35 USC § 102

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-4 and 6 are rejected under 35 U.S.C. 102(a) as being anticipated by Lu et al. (Int. J. Cancer January 2002 vol. 97, p.393-399).

The Claims are drawn to isolated human antibody or fragment thereof which binds selectively to KDR and inhibits binding of VEGF to KDR.

Lu et al. teach several isolated high-affinity human Fab antibody fragments directed against KDR from an antibody phage display library. These human Fab fragments bind specifically to KDR and block KDR/VEGF interaction (see p. 398, right column, lines 8-12). Figure 1 of Lu et al. discloses the CDR sequences of several

human Fab clones. These sequences are identical to SEQ ID NOs: 1-18 and teach the same CDR sequences in each clone. Therefore the reference teaches each and every limitation of the claims.

7. Claims 1-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Rockwell et al. (WO/2002/070008 March 2, 2001)

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The Claims are drawn to an isolated human antibody or fragment thereof which binds selectively to KDR, an isolated polynucleotide that encodes said antibody, an expression vector comprising said polynucleotide, and a recombinant host cell comprising said expression vector.

Rockwell et al. teach VEGF receptor antagonists (disclosed as anti-KDR see example 12) used to reduce or inhibit tumor growth in a mammal. Rockwell et al. teach the polynucleotides, expression vectors, and host cells needed to prepare the antibodies of the invention. Rockwell et al. also disclose the antibody fragments listed in Claim 2 (see section [98] of Rockwell et al.).

The SEQ ID NOs disclosed in the instant application are identical to the SEQ ID NOs disclosed in Rockwell et al. (see table 3 and 4). The reference teaches each and every limitation of the claimed invention.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken et al. (Cancer Research Vol. 60 p.5117-5124, Sept. 2000) in view of Kucherlapati et al. (US Patent 6075181).

9. The claims are drawn to a human antibody or fragment thereof which binds selectively to KDR (also know as VEGFR-2, see specifications p. 7, line 11) and inhibits binding of VEGF to KDR.

10. Brekken et al. teach a mouse monoclonal antibody, 2C3, which blocks the interaction of VEGF with VEGFR-2 (also known as KDR) but not with VEGFR1 (see

Results p. 5119, left column). The 2C3 antibody was also shown to have potent anti-tumor activity, inhibiting the growth of newly injected and established human tumor xenografts in mice (see Fig. 5, p.5121). Brekken et al. suggest that 2C3 antibody and other anti-VEGF therapies exert their anti-tumor activation by preventing vascular remodeling and endothelial cell survival in addition to preventing endothelial cell proliferation in tumors. The finding that 2C3 suppressed tumor growth indicates a dominant role for VEGFR2 in promoting tumor angiogenesis. Brekken et al. does not teach a *human* antibody or fragment thereof which binds selectively to KDR and inhibits binding of VEGF to KDR. This deficiency is made up for in Kucherlapati et al.

11. Kucherlapati et al. teach a method of preparing antibodies with fully human variable regions against a specific antigen by administering the antigen to a transgenic animal which has been modified to produce such antibodes in response to antigenic challenge, but whose endogenous loci have been disabled.

12. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a human 2C3 antibody, which blocks the interaction of VEGF with VEGFR-2, by the methods taught in Kucherlapati et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings in Kucherlapati et al. to make a human 2C3 antibody based on the findings of Brekken et al. that the 2C3 antibody had potent anti-tumor activity *in vivo* and could potentially be used for therapy.

Therefore, the invention as a whole is obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the reference.

Conclusion

13. Claims 1-17 are rejected.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meera Natarajan whose telephone number is 571-270-3058. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

MN

Current Application Sequences

between VEGF and KDR. Three were KDR-specific binders and one cross-reacted with Flk-1. DNA fingerprinting and sequencing analysis confirmed that all four KDR/VEGF blocking antibodies were different (Fig. 1A) with unique DNA and amino acid sequences.

[0101] The amino acid sequences for CDR1, CDR2 and CDR3 of V_H and V_L for the four clones are given in Table 1.

Table 1 - CDR sequences of selected KDR-binding human Fabs

Clone	CDR1	CDR2	CDR3
Light Chain			
D2C6	RASQSVSSYLA (SEQ ID NO:1)	DSSNRAT (SEQ ID NO:2)	LQHNTFPPT (SEQ ID NO:3)
D2H2	RASQGISSRLA (SEQ ID NO:4)	AASSLQT (SEQ ID NO:5)	QQANRFPPT (SEQ ID NO:6)
D1H4	AGTTTDLTYYDLVS (SEQ ID NO:7)	DGNKRPS (SEQ ID NO:8)	NSYVSSRFYV (SEQ ID NO:9)
D1F7	SGSTSNIGTNTAN (SEQ ID NO:10)	NNNQRPS (SEQ ID NO:11)	AAWDDSLNGHWV (SEQ ID NO:12)
Heavy Chain			
D2C6	GFTFSSYSMN (SEQ ID NO:13)	SISSSSSYIYYADSVKG (SEQ ID NO:14)	VTDAFDI (SEQ ID NO:15)
D2H2	GFTFSSYSMN (SEQ ID NO:13)	SISSSSSYIYYADSVKG (SEQ ID NO:14)	VTDAFDI (SEQ ID NO:15)
D1H4	GFTFSSYSMN (SEQ ID NO:13)	SISSSSSYIYYADSVKG (SEQ ID NO:14)	VTDAFDI (SEQ ID NO:15)
D1F7	GGTFSSYAIS (SEQ ID NO:16)	GGIIPIFGTANYAQKFQG (SEQ ID NO:17)	GYDYYDSSGVASPFDY (SEQ ID NO:18)

Complete sequences for the V_H and V_L chains are presented in the Sequence Listing. For D1F7, the nucleotide and amino acid sequences for V_H are represented by SEQ ID NOS:19 and 20 respectively, and the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 21 and 22.

[0102] For D2C6, the nucleotide and amino acid sequences for V_H are represented by SEQ ID NOS: 23 and 24 respectively, and the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 25 and 26.

[0103] For D2H2, the nucleotide and amino acid sequences for V_H are represented by SEQ ID NOS: 30 and 31 respectively, and the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 32 and 33.

[0104] For D1H4, the nucleotide and amino acid sequences for V_H are represented by SEQ ID NOS: 27 and 24 respectively, and the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 28 and 29.

[0105] A second library was created combining the single heavy chain of D2C6 with a diverse population of light chains derived from the original library. Ten additional Fabs were identified, designated SA1, SA3, SB10, SB5, SC7, SD2, SD5, SF2, SF7, and 1121. The nucleotide and amino acid sequences for V_L of the ten Fabs are represented as follows. For SA1, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 34 and 35. For SA3, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 36 and 37. For SB10, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 38 and 39. For SB5, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 40 and 41. For SC7, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 42 and 43. For SD2, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 44 and 45. For SD5, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 46 and 47. For SF2, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 48 and 49. For SF7, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 50 and 51. For 1121, the nucleotide and amino acid sequences for V_L are represented by SEQ ID NOS: 52 and 53.

[0106] The V_L CDR sequences are presented in Table 2.

Table 2 - Light chain CDR sequences of KDR-binding human Fabs			
Clone	CDR1	CDR2	CDR3
SA1	TGSHSNFGAGTDV (SEQ ID NO:54)	GDSNRPS (SEQ ID NO:55)	QSYDYGLRGWV (SEQ ID NO:56)
SA3	RASQNINNYLN (SEQ ID NO:57)	AASTLQS (SEQ ID NO:58)	QQYSRYPPT (SEQ ID NO:59)
SB10	TGSSTDVGNYNYIS (SEQ ID NO:60)	DVTSRPS (SEQ ID NO:61)	NSYSATDTLV (SEQ ID NO:62)
SB5	TGQSSNIGADYDVH (SEQ ID NO:63)	GHNNRPS (SEQ ID NO:64)	QSYDSSLSGLV (SEQ ID NO:65)
SC7	RASQDISSWLA (SEQ ID NO:66)	AASLLQS (SEQ ID NO:67)	QQADSFPPT (SEQ ID NO:68)
SD2	RASQSIKRWLA (SEQ ID NO:69)	AASTLQS (SEQ ID NO:70)	QQANSFPPT (SEQ ID NO:71)
SD5	SGSRSNIGAHYEVQ (SEQ ID NO:72)	GDTNRPS (SEQ ID NO:73)	QSYDTSLRGPV (SEQ ID NO:74)
SF2	TGSSSNIGTGYDVH (SEQ ID NO:75)	AYTNRPS (SEQ ID NO:76)	QSFDDSLNGLV (SEQ ID NO:77)
SF7	TGSHSNFGAGTDVH (SEQ ID NO:78)	GDTHRPS (SEQ ID NO:79)	QSYDYGLRGWV (SEQ ID NO:80)
1121	RASQGIDNWLG (SEQ ID NO:81)	DASNLDT (SEQ ID NO:82)	QQAKAFPPT (SEQ ID NO:83)

Example II. Assays

Example II(a). ***Quantitative KDR binding and blocking of KDR/VEGF interaction.***

[0107] In a direct binding assay, various amounts of soluble Fab proteins were added to KDR-coated 96-well Maxi-sorp microtiter plates and incubated at RT for 1 h, after which the plates were washed 3 times with PBST. The plates were then incubated at RT for 1 h with 100 μl of a rabbit anti-human Fab antibody-HRP conjugate (Jackson ImmunoResearch Laboratory Inc., West Grove, PA). The plates were washed and developed following the procedure described above for the phage ELISA. In a competitive KDR/VEGF blocking assay, various amounts of Fab proteins were mixed with a fixed amount of KDR-AP